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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,899	09/26/2005	Peter John Meikle	128675.00011 (MAYO-0001 W)	5695
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JACKSON WALKER LLP 901 MAIN STREET SUITE 6000 DALLAS, TX 75202-3797			XU, XIAOYUN	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/517,899	<b>Applicant(s)</b> MEIKLE ET AL.	
	<b>Examiner</b> ROBERT XU	<b>Art Unit</b> 1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 10 December 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-61 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-61 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>03/17/2008, 08/28/2006, 10/11/2005, 06/30/2005</u> .          | 6) <input type="checkbox"/> Other: _____                          |



## DETAILED ACTION

### ***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

2. **Claims 1-6, 12, 13, 15-19, 21, 24, 27, 28, 30-32, 38, 39, 40-44, 46, 49, 52-54, 56 and 58-60** are rejected under 35 U.S.C. 102(a) as being anticipated by Rozaklis et al. (Clinical Chemistry, 2002, IDS) (Rozaklis).

In regard to Claim 1, Rozaklis teaches a method for diagnosing a pre-clinical status, or a clinical status of a mucopolysaccharidoses ("MPS") disease in a target patient comprising:

(a) determining a target quantity of a target MPS biomarker from a target biological sample taken from the target patient (see abstract, Table 1-3); and

(b) comparing the target quantity to a reference quantity of a reference MPS biomarker (see abstract, Table 1-3);

wherein,

the target MPS biomarker is the same or equivalent to the reference MPS biomarker, and each of the target MPS biomarker and the reference MPS biomarker is an oligosaccharide (see abstract);

the reference quantity is determined from a reference human, or group of reference human, having a known MPS clinical status (see Table 1-3);

the target quantity and the reference quantity are determined by a mass spectrometric analysis (see page 134, right col. 4<sup>th</sup> paragraph); and

a deviation of the target quantity of the target MPS biomarker from the reference quantity of the reference MPS biomarker is a pre-clinical or clinical indication of the MPS disease, an indication of a progression of the MPS disease, or an indication of a regression of the MPS disease (see page 138, left col.).

In regard to Claim 27, Rozaklis teaches a method for diagnosing a preclinical status, or a clinical status, of a mucopolysaccharidoses ("MPS") disease in a target animal comprising:

- (a) derivatizing a target MPS biomarker with a derivatizing agent forming a derivatized target MPS biomarker (see page 134, left col. 2<sup>nd</sup> paragraph);
- (b) binding the derivatized target MPS biomarker to an extraction compound to give a bound derivatized target MPS biomarker (see page 134, left col. 2<sup>nd</sup> paragraph);
- (c) eluting the bound derivatized target MPS biomarker from the extraction compound with an elution solution forming an eluted target MPS biomarker (see page 134, left col. 2<sup>nd</sup> paragraph);
- (d) determining a target quantity of the eluted target MPS biomarker (see page 134, right col.); and
- (e) comparing the target quantity with a reference quantity of a reference MPS biomarker (see page 134, right col., Table 1-3);

wherein,

the target MPS biomarker was obtained from a biological sample of a target human having the MPS biomarker contained (see page 132, left col. least paragraph, right col.) therein;

the target MPS biomarker is the same or equivalent to the reference MPS biomarker, and each of the target MPS biomarker and the reference MPS biomarker is an oligosaccharide (see Table 1-3);

the reference quantity is determined in a reference human, or group of reference human having a known MPS clinical status (see Table 1-3); and

a deviation in the quantity of the eluted target MPS biomarker when compared to the reference quantity is a pre-clinical or clinical indication of the MPS disease, a progression of the MPS disease, or a regression of the MPS disease (see page 138, left col.).

In regard to Claims 2 and 28, Rozaklis teaches that the target biological sample or reference biological sample is selected from urine, plasma, or blood (see abstract).

In regard to Claim 3, Rozaklis teaches derivatizing the target MPS biomarker and the reference MPS biomarker with a derivatizing agent prior to determining the quantity of the target MPS biomarker or the quantity of the reference MPS biomarker (see page 134, left col., right col. 1<sup>st</sup> paragraph).

In regard to Claims 4 and 30, Rozaklis teaches that the derivatizing agent is 1-phenyl-3-methyl-5-pyrazolone ("PMP") (see page 134, left col., right col. 1<sup>st</sup> paragraph).

In regard to Claims 5 and 31, Rozaklis teaches that the oligosaccharide comprises a sulfated saccharide molecule having a sugar length ranging from 1 to 12 residues (see Table 1-3).

In regard to Claims 6 and 32, Rozaklis teaches that the oligosaccharide identified from the target biological sample comprises a cleavage product of a glycosaminoglycan ("GAG") (see Table 1-3).

In regard to Claim 12, Rozaklis teaches that the mass spectrometry comprises electrospray-ionization tandem mass spectrometry ("ESI-MSMS") or liquid chromatography tandem mass spectrometry ("LC-MSMS") (see page 134, right col., Figure 4).

In regard to Claims 13 and 39, Rozaklis teaches that the mass spectrometry is carried out in conjunction with HPLC or an immunoassay (see page 132 left col. 2<sup>nd</sup> paragraph).

In regard to Claims 15-18, 40, 41, 43 and 44, Rozaklis teaches that MPS can be treated with enzyme-replacement therapy (see page 132, left col. 1<sup>st</sup> paragraph). Therefore, monitoring and adjusting the treatment of MPS is inherently the function and goal of Rozaklis' method.

In regard to Claims 19, 21, 42 and 46, Rozaklis teaches that the target biological sample and the reference biological sample contain MeLac as an internal standard. MeLac is a non-physiological oligosaccharide that is similar to the oligosaccharide being investigated (see page 137, right col. 3<sup>rd</sup> paragraph).

In regard to Claims 24 and 49, Rozaklis teaches that the target is an infant (see Table 2).

In regard to Claim 38, Rozaklis teaches that determining the target quantity comprises a mass spectrometric analysis (see page 134, right col.).

In read to Claim 52, Rozaklis teaches a kit (materials) for diagnosing a pre-clinical status, or a clinical status of a mucopolysaccharidoses ("MPS") disease in a target animal comprising:

- (a) an oligosaccharide derivatization agent (1-phenyl-3-methyl-5-pyrazolone (PMP)) (see page 132, right col. 5<sup>th</sup> paragraph);
- (b) an acid solution (formic acid) (see page 132, right col. 5<sup>th</sup> paragraph);
- (c) an internal standard (MeLac) (see page 132, right col. 5<sup>th</sup> paragraph);
- (d) a solid phase extraction column (C18 reverse-phase extraction column)(see page 132, right col. 5<sup>th</sup> paragraph);
- (e) a solid phase extraction column wash solution ( $\text{CHCl}_3$ ) (see page 132, right col. 5<sup>th</sup> paragraph); and
- (f) an oligosaccharide elution solution ( $\text{CH}_3\text{CN}$ /formic acid) (see page 132, right col. 5<sup>th</sup> paragraph).

In regard to Claim 53, Rozaklis teaches that the oligosaccharide derivatization agent is a solution comprising: 1-phenyl-3methyl-5-pyazolone (PMP) (see page 134, left col.).

In regard to Claim 54, Rozaklis teaches that the acid solution comprises formic acid (see page 134, left col.).

In regard to Claim 56, Rozaklis teaches that the internal standard comprises a non-physiological oligosaccharide that is similar to the oligosaccharide being investigated (see page 137, right col.).

In regard to Claim 58, Rozaklis teaches that the solid phase extraction column comprises a C18 reverse phase column (see page 134, left col.).

In regard to Claim 59, Rozaklis teaches that the solid phase extraction column wash solution comprises:  $\text{CHCl}_3$  (see page 134, left col.).

In regard to Claim 60, Rozaklis teaches that the oligosaccharide elution solution comprises:  $\text{CH}_3\text{CN}$  and formic acid (see page 134, left col.).

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. **Claims 22, 47 and 57** are rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis.

In regard to Claims 22, 47 and 57, Rozaklis does not specifically teach that the internal standard is the non-physiological oligosaccharide derived from a chondroitinase digestion of chondroitin sulfate having an unsaturated uronic acid at the non-reducing end. The applicant is advised that the Supreme Court recently clarified that a claim can be proved obvious merely by showing that the combination of known elements was obvious to try. In this regard, the Supreme Court explained that, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has a good reason to pursue the known options within his or her technical grasp." An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of the case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. The combination of familiar elements is likely to be obvious when it does no more than yield predictable results. (See *KSR Int'l v. Teleflex Inc.*, 127 Sup. Ct. 1727, 1742, 82 USPQ2d



1385, 1397 (2007)). In that regard, Rozaklis teaches that when suitable labeled isotopes are not readily available for oligosaccharides, one can use a non-physiologic oligosaccharide as an internal standard (see page 137, right col. 3<sup>rd</sup> paragraph). Therefore, at the time of the invention it would have been obvious to ordinary skill in the art to use non-physiologic oligosaccharide derived from a chondroitinase digested chondroitin sulfate (CS) having an unsaturated uronic acid at the non-reducing end, because this non-physiologic oligosaccharide derived from CS does no more than being an internal standard in mass spectrometry calibration as taught by Rozaklis.

6. **Claims 7, 23, 25, 26, 33, 48, 50 and 51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Byers, et al. (Molecular Genetics and Metabolism, 1998, IDS) (Byers).

In regard to Claims 7 and 33, Rozaklis does not explicitly clarify that the GAG is heparan sulfate, dermatan sulfate, keratan sulfate, or chondroitin sulfate. However, the GAG being heparan sulfate, dermatan sulfate, keratan sulfate, or chondroitin sulfate is well known in the art. Byers teaches that the Glycosaminoglycans (GAG) accumulated and excreted in the mucopolysaccharidoses is heparan sulfate, dermatan sulfate, keratan sulfate, or chondroitin sulfate (see page 282, right col. 1<sup>st</sup> paragraph). At time of the invention, one of ordinary skill in the art would have recognized that the GSG analyzed by Rozaklis is heparan sulfate, dermatan sulfate, keratan sulfate, or chondroitin sulfate based on Byers' teaching.

In regard to Claims 23 and 48, Rozaklis teaches that the MPS disease includes MPS-III, and MPS-VI (see page 132, left col. 2<sup>nd</sup> paragraph). Byers teaches that MPS includes I, II, IIIA, IIIB, IIIC, IIID, IVA and VI subtypes (see page 282, right col.). At the time of the invention it would have been obvious for ordinary skill in the art to include I, II, IIIA, IIIB, IIIC, IIID, IVA and VI as subtype of MPS as taught by Byers in Rozaklis' method.

In regard to Claims 25, 26, 50 and 51 Rozaklis does not specifically teach that the target MPS biomarker is contacted with an enzyme that characterizes a particular MPS disease subtype before determining the target quantity. Byers teaches contacting the target MPS biomarker with an enzyme ( $\alpha$ -L-iduronidase) that characterizes a

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particular MPS disease subtype before determining the target quantity (see page 283, right col. last paragraph). Byers derives results by comparing the quantity of GAG analysis before and after the enzyme digestion. At the time of the invention, it would have been obvious to one of ordinary skill in the art to contacting the target MPS biomarker with an enzyme ( $\alpha$ -L-iduronidase) that characterizes a particular MPS disease subtype before determining the target quantity as taught by Byers, so that the subtype of MPS can be determined.

7. **Claim 14** is rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Leeuwenburgh et al. (The American Physiological Society, 1999) (Leeuwenburgh).

In regard to Claim 14, Rozaklis does not specifically teach that the target quantity and the reference quantity are normalized to creatinine or another oligosaccharide. Normalizing the quantity of the mass spectrometry result is routinely performed in the art to correct individual differences of the samples. For example, Leeuwenburgh teaches normalizing the result of mass spectrometry to urine level of creatinine to correct individual differences of samples (see page R130, right col. 1<sup>st</sup> paragraph). At the time of the invention, it would have been obvious to one of ordinary skill in the art to use the urine level of creatinine to normalize the urine level of GAG in MS, so that the individual sample differences can be corrected.

8. **Claims 20, 45 and 55** are rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Hopwood et al. (Biochemical Journal, 1985, IDS) (Hopwood).

In regard to Claims 20, 45 and 55, Rozaklis teaches that using stable-isotope as an internal standard is the best method for accurate quantification of compounds in biological sample in MS analysis (see page 137, 3<sup>rd</sup> paragraph). Hopwood teaches that GlcNAc6S is found in abnormal amount in the urine of a patient with MPS IIID (see page 229, right col.). Therefore, a deuterated N-acetylglucosamine-6-sulfate ("GlcNAc6S(d3)") will be an obvious choice of internal standard for mass spectrometry analysis in Rozaklis' method.

9. **Claims 8-11 and 34-37** are rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Byers as applied to claims 7, 23, 25, 26, 33 above, and further in view of Merry et al. (The Journal of Biological Chemistry, 1999) (Merry).

In regard to Claims 8-11 and 34-37, Byers teaches that Glycosaminoglycans (GAGs) contains linkages of N-acetylgalactosamine-glucuronic acid (GlcA-GalNAc-) and N-acetylgalactosamine-iduronic acid (IdoA-GalNAc-) (see page 288, left col.). Merry teaches that iduronic acid (IdoA) is the major uronic acid component of the GAGs dermatan sulfate and heparan sulfate (see Figure 2). Therefore, at time of the invention it would have been obvious to one of ordinary skill in the art to recognize that the fragments of dermatan sulfate, heparan sulfate, keratan sulfate and chondroitin sulfate comprise combination of iduronic acid (IdoA), N-acetylgalactosamine (GalNAc), uronic acid (UA), glucuronic acid (GlcA) and sulfate (S).

10. **Claim 61** is rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Byers, Hopwood, Leeuwenburgh and Merry.

In regard to Claim 61, Rozaklis teaches a method for diagnosing a pre-clinical status, or a clinical status, of a mucopolysaccharidoses ("MPS") disease in a target animal comprising:

(a) determining a target quantity of a target MPS biomarker from a target biological sample taken from the target animal (see page 134); and

(b) comparing the target quantity to a reference quantity of a reference MPS biomarker (see Table 1-3);

Rozaklis teaches that the target MPS biomarker is the same or equivalent to the reference MPS biomarker (see Table 1-3), and each of the target MPS biomarker and the reference MPS biomarker is an oligosaccharide (see page 134),

Rozaklis teaches that the target MPS biomarker and the reference MPS biomarker are derivatized with a derivatizing agent prior to determining the quantity of the target MPS biomarker and the quantity of the reference MPS biomarker, wherein, the derivatizing agent comprises 1-phenyl-3-methyl-5-pyrazolone ("PMP") (see page 134);

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Rozaklis teaches that the reference quantity is determined from a reference human, or group of reference human, having a known MPS clinical status (see page 132);

Rozaklis teaches that a deviation of the target quantity from the reference quantity is a pre-clinical or clinical indication of the MPS disease, an indication of a progression of the MPS disease, or an indication of a regression of the MPS disease see page 138),

Rozaklis teaches that the target quantity and the reference quantity are determined using a mass spectrometry method (see [age 134); and

As has been discussed in regard to claims 8-11 and 34-37, Rozaklis-Byers teaches that oligosaccharide comprises: HNAcS; HNAcS<sub>2</sub>; HNS-UA; UA-HNAcS; HNAcS-UA; UA-HNAc-UA-S; (HNAc-UA)<sub>2</sub>-S; (HNAc-UA)<sub>2</sub>(S)<sub>2</sub>; or hexasac.

As has been discussed in regard to Claim 14, Rozaklis- Leeuwenburgh teaches normalizing the result of mass spectrometry to urine level of creatinine to correct individual differences of samples (see page R130, right col. 1<sup>st</sup> paragraph).

As has been discussed in regard to Claims 23 and 48, Rozaklis-Byers teaches that the MPS disease is selected from a group comprises: MPS I, MPS II, MPS IIIA, MPS IIIB, MPS IIIC, MPS IIID, MPS IVA, MPS VI, or multiple sulfatase deficiency;

As has been discussed in regard to Claims 20, 45 and 55, Rozaklis-Hopwood teaches that an internal standard is utilized to accurately determine the target quantity and the reference quantity, wherein the internal standard comprises a deuterated N-acetylglucosamine-6-sulfate ("GlcNAc6S(d<sub>3</sub>)").

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

3/15/2009

/Yelena G. Gakh/  
Primary Examiner, Art Unit 1797

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